Genetics of Asthma and Hay Fever in Australian Twins[1-3]

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SUMMARY The occurrence of self-reported asthma/wheezing and hay fever among 3,808 pairs of twins from the Australian National Health and Medical Research Council Twin Registry was examined for evidence of genetic transmission by path analytic methods. The cumulative prevalence of asthma or wheezing was 13.2% and of hay fever, 32%. There were significant correlations in liability to reported disease among twins, and these were higher in monozygotic twins (MZ) ($r = 0.65$) than in dizygotic twins (DZ) ($r = 0.25$), and in male MZ twins ($r = 0.75$) compared with female MZ twins ($r = 0.60$). Analysis under the assumptions of the classic twin model suggested that there were genetic factors common to asthma and hay fever, with a correlation in genetic liability to the traits of 0.52 for men and 0.65 for women. These genes acted substantially in a nonadditive fashion in men but not in women. As the genetic correlation was significantly less than unity, this implied additional genetic factors influencing either or both diseases individually. The estimated heritability of these diseases was 60 to 70% in this population. Environmental causes of both diseases also were correlated ($r = 0.53$ for men and 0.33 for women). Cigarette smoking was only weakly associated with wheezing.

AM REV RESPIR DIS 1990; 142:1351-1358

Introduction

Asthma and hay fever are diseases in which it is known that allergic- or immunoglobulin E (IgE)-mediated processes play an important role (1). Both of these diseases are common in Australia. Asthma affects as much as 20% of the population during childhood (2, 3) and 5 to 10% at some time in their adult lives (4). Hay fever has been reported to have a cumulative prevalence of approximately 30% in Australian children (5).

It has long been recognized that both asthma and hay fever tend to cluster in families, but studies of the inheritance of these diseases have produced conflicting results (6). In view of their known associations in individuals and families, and the fact that attacks of both can be provoked by exposure to allergens, these diseases have been seen as expressions of a general tendency in the individual to such allergic processes. This tendency is usually termed "atopy," and its presence in the individual is identified by the presence of markers such as positive skin prick testing or elevated serum IgE levels. It is this underlying predisposition that is commonly accepted as heritable (7). Only a few studies have been undertaken to explore the possibility of genetic influences unique to the expression of asthma or hay fever alone (8-12).

One of the most informative studies of the genetics of these two main allergic expressions was the large twin study performed by Edfors-Lub in Sweden (12). The present research uses the method of path analysis to analyze data on self-reported asthma or wheeze and hay fever in a large Australian twin sample.

Methods

In the period from November 1980 to March 1982, a questionnaire was mailed to all 5,967 pairs of twins registered with the Australian National Health and Medical Research Council Twin Registry who were older than 18 yr of age. These pairs were volunteers who had been recruited through schools, through community groups, and by media advertising throughout Australia. Of this group, 3,808 twin pairs returned completed questionnaires (a response rate of 64%). There was an individual response rate of 75%, suggesting little or no concordance for nonresponse.

The questionnaire was extensive and included items on age, sex, zygosity, birth order, tobacco use, psychologic traits, and a number of physical and psychiatric symptoms. Zygosity of the twins was diagnosed by response to a number of items, supplemented in ambiguous cases by examination of photographs sent in by the twins. This method was shown to be at least 95% accurate in several other studies (13).

The physical symptom checklist was prefaced, "How often have you had any of the following?" and included "hay fever" and "asthma or wheezing." Responses fell into four categories: never, only as a child, rarely, quite often. For the purposes of the current analysis, the last three responses have been combined into ever versus never. Because 25% of the pairs had left one or more of these two items blank, the overall response to the 22-item physical symptom checklist was reexamined. This revealed that only 19 of 7,616 individuals left the table entirely uncompleted. Furthermore, many respondents only indicated the positive items that referred to them and left the remainder blank. It was therefore decided to score all blank responses as never. As a check, prevalences and correlations including and excluding the missing values were calculated. Only negligible differences were found.

For analysis, the subjects were divided into five zygosity groups: monozygotic (MZ) women (1,232 pairs), MZ men (567 pairs), dizygotic (DZ) women (751 pairs), DZ men (352 pairs), and DZ female-male (906 pairs) (table 1). Analysis was performed under the assumptions of the multifactorial threshold model, a model that has been applied with success to a number of genetic diseases (14, 15). It assumes that there is a continuous gradation of risk of being affected by a disease in the population and that this risk is determined by an individual's liability (or susceptibility), a value on a single underlying causative dimension. The liability is the sum of the effects due to many genetic and environmental factors, and so is usually thought of as being normally distributed in the population, although models can be derived that allow the presence of a major gene with a substantial influence on the risk of being affected, so-called mixed models (16). Individuals are affected by the disease when they exceed the threshold of affectation on the liability distribution (figure 1).

(Received in original form December 29, 1989 and in revised form May 2, 1990)

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TABLE 1

SELF-REPORTED PRESENCE (+) AND ABSENCE (−) OF ASTHMA AND HAY FEVER IN 3,808 PAIRS OF ADULT TWINS

		Asthma: Number of Pairs and Percentage Affected				Hay Fever: Number of Pairs and Percentage Affected			
Zygosity Group	n:	+ +	+ −	− +	− −	+ +	+ −	− +	− −
MZ women, n = 1,232 pairs	n:	67	87	98	980	257	163	174	638
	%:	5.4	7.1	7.9	79.5	20.9	13.2	14.1	51.8
MZ men, n = 567 pairs	n:	39	33	31	464	99	71	63	334
	%:	6.9	5.8	5.5	81.8	17.5	12.5	11.1	58.9
DZ women, n = 751 pairs	n:	19	67	69	596	106	138	123	384
	%:	2.5	8.9	9.2	79.4	14.1	18.4	16.4	51.1
DZ men, n = 352 pairs	n:	12	43	39	258	34	68	68	182
	%:	3.4	12.2	11.1	73.3	9.7	19.3	19.3	51.7
DZ woman/man, n = 906 pairs	n:	32	105	98	671	125	181	153	447
	%:	3.5	11.6	10.8	74.1	13.8	20.0	16.9	49.3

The genetic liability to a disease is divisible into two statistical components: additive and nonadditive. The additive genetic component is due to a gene or genes that causes the risk to increase linearly with the presence of zero, one, or two alleles at the particular locus. The nonadditive component is due to the nonlinear interaction of alleles either at the same locus (a classic Mendelian dominant or recessive gene) or at two or more different loci (epistasis). In a classic twin study, these two latter possibilities cannot be separated, and in fact, it is difficult to obtain evidence of the presence of epistasis in humans (17, 18).

Among MZ twins, any resemblances in the observed (i.e., phenotypic) expression of disease must be attributable either to genes or to shared environmental exposures. Any dissimilarities must be caused by environmental influences that have affected one twin but not the other (this includes errors in diagnosis or reporting). Because MZ twins have identical genomes, the correlation between their genetic liabilities must be unity. DZ twins, by contrast, are no more closely related genetically than are ordinary siblings. It can be shown that the expected correlation between their additive contributions to genetic liability is 0.5, but between their nonadditive genetic components of liability, it is only 0.25 (19).

In studies observing twins who have been reared together, the correlation in liability due to shared environment is usually assumed to be the same in MZ and DZ twin families—the homogeneity of environment assumption. This has been shown to be valid for a number of traits examined to date (20). Differences in the observed correlations among the different types of twins must then be attributed to differences in genetic variance of liability, the amount due to additive and nonadditive genetic components depending on the magnitude of the difference between the MZ and DZ groups. It is this ability to partition liability using a priori knowledge about genetic transmission that makes this approach more powerful than other methods of comparing MZ and DZ concordance rates for a disease (12, 21).

For the purposes of this report, the correlations between the presence or absence of hay fever and asthma/wheezing, and age within each zygosity group are expressed as tetrachoric or biserial correlation coefficients using the program PRELIS (22). The tetrachoric correlation coefficient is the Pearsonian intraclass correlation coefficient, assuming that the two marginal categories (ever and never) reflect a normal, continuous liability distribution divided in two by a threshold.

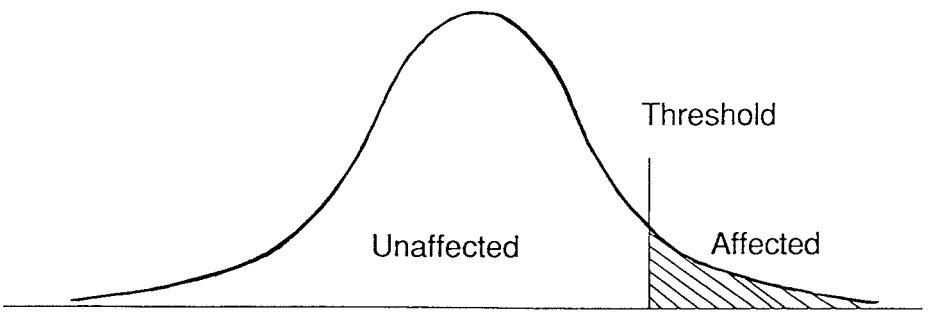

Fig. 1. The population liability distribution. Individuals above the threshold have a sufficiently high "dose" to express a disease. (The threshold model can be shown to be equivalent to a probitlike model where lifetime morbid risk of affection is a cumulative, normal function of liability, and the mean liability is a function of disease prevalence.) From the prevalence of a trait, the z-deviate of the threshold can be determined for the general population and compared to that found among the relatives of probands.

The biserial r correlates such a latent liability distribution with a continuous variable such as age.

A number of path analytic models of inheritance of hay fever and asthma have been fitted to the data by a weighted least squares (WLS) approach, using the program LISREL 7.16 (23). These models set the expected correlations between the different components of liability to those described above (figure 2). Initially, a "full" model using an additive genetic component, a nonadditive genetic component or a shared environmental component, and a unique (individual-specific) environmental component is fitted to the observed phenotypic correlations. Only one of these two possible full models can be fitted to a given set of twin data because if the correlation due to shared environment (c^2) is more than half that due to genetic nonadditivity (d^2), the estimate for d is negative, whereas if $c^2 < \frac{1}{2}d^2$, then c will be estimated to be negative. The adequacy of fit is examined by large sample (likelihood ratio) χ^2 test. Submodels excluding various components are then examined and compared to the full models by hierarchic χ^2 tests. The model using the smallest number of different parameters to reproduce accurately the observed correlations is accepted as the "best" model (that is, the simplest explanation of the data).

Another measure we report is the "broad sense" heritability or coefficient of genetic determination, which is the proportion of total variation of liability attributable to genetic factors. This is calculated from the path coefficients (figure 2) as the following:

$$H_b = (h^2 + d^2)/(h^2 + d^2 + e^2) \text{ or } h^2/(h^2 + c^2 + e^2)$$

It is important to realize that this proportion can vary not only from population to population but from time to time and measures only the relative importance of genetic and environmental influences.

Results

Reliability of Questionnaire Items

Consistency of responses was examined in a group of 100 individuals who completed the questionnaire on two occasions, on average four months apart. For the "asthma or wheezing" item (hereafter referred to simply as asthma), the reliability tetrachoric r was 0.98 (95% confidence interval [CI], 0.93–1.00), representing three changes in reported disease status from the first to the second occasion; for reported hay fever, it was 0.94 (95% CI, 0.87–1.00), representing 11 changes. Because the sample size was less than 200, these asymptotic confidence limits should be interpreted with caution (22).

Prevalence of Reported Symptoms: Age and Sex Associations

The ages of twins in the study ranged

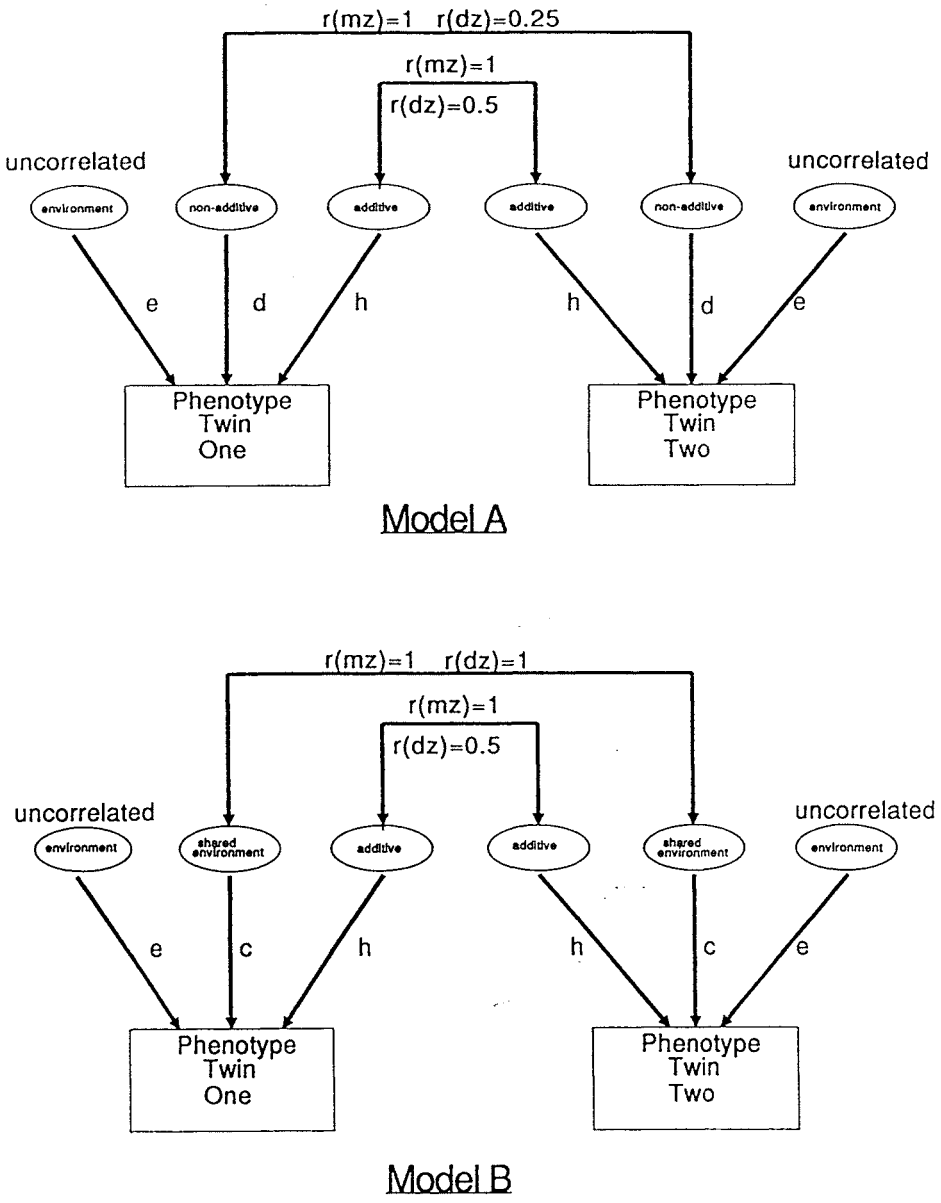

Fig. 2. Path diagram of univariate model. Path coefficients h, d, c, and e are equivalent to standardized partial regression coefficients. Therefore two alternative models can be written (as d and c cannot be estimated simultaneously): Model A (Phenotypic liability) = h (additive genetic component) + d (nonadditive genetic component) + e (individual specific environment). Model B (Phenotypic liability) = h (additive genetic component) + c (shared environmental component) + e (individual specific environment) where $h^2 + d^2 + e^2 = 1$ or $h^2 + c^2 + e^2 = 1$. In these models, the proportion of variability due to each component is the square of its respective path coefficient.

from 18 to 88 yr; however, the median age was only 32 yr. The mean age was 36.5 yr (men, 35.4; women, 37.1; SD = 14.2 yr). There were small differences in mean age of the different zygosity groups, ranging from 34.2 (DZ men) to 37.8 yr (MZ women).

Of all individuals, 13.2% reported ever having suffered asthma. There was a small male preponderance in reported asthma (men, 13.8%; women, 12.9%; $\chi^2_1 = 1.1$, $p = 0.30$). Significantly more women reported hay fever than did men (men, 29.7%; women, 33.4%; $\chi^2_1 = 11.6$, $p < 0.001$). There were small differences in reported cumulative prevalence across the five zygosity groups with the MZ women reporting significantly more hay fever than did the DZ women (34.5 versus 29.3%; $\chi^2_1 = 9.74$, $p = 0.002$); the DZ men reported more asthma than did the MZ men (15.1 versus 11.6%; $\chi^2_1 = 5.2$, $p = 0.02$).

There were no significant differences between the firstborn twin and the second born twin in prevalence of asthma or hay fever in either the MZ or DZ groups, thus excluding major effects of birth trauma or twin-twin transfusion on the second born twin.

To examine the effects of age on cumulative prevalence, we divided the group into three equally sized age cohorts: 25 yr of age or less, 26 to 35 yr of age, older than 35 yr of age. Age had no significant effect on reported prevalence of asthma ($\chi^2_2 = 0.26$). There was a statistically significant, but small, effect of age on hay fever, with the range of prevalences being 30 to 33.7% within the three cohorts ($\chi^2_2 = 6.8$, $p = 0.03$). In addition, the biserial correlations between reported symptoms and age were examined. These showed small, nonsignificant negative correlations.

Cigarette smoking was scrutinized as another possible confounding variable. Nonsmokers comprised 60.4% of the women and 50% of the men. Men also smoked a greater number of cigarettes per day, especially DZ men. Total pack-years smoked did not predict asthma status. Ever versus never smoking was weakly associated with asthma (odds ratio = 1.2; 95% CI, 1.04–1.36). Similarly, both cigarettes consumed per day and lifetime maximal daily cigarette intake were associated with increasing incidence of asthma or wheeze, with an overall age-sex adjusted odds ratio of 1.45 (95% CI, 1.2–1.6) of asthma, comparing nonsmokers to those smoking more than 30 cigarettes per day. This agreed well with the equivalent biserial correlation of 0.09 between asthma and daily cigarette consumption (95% CI, 0.07–0.13) as estimated using PRELIS.

Tetrachoric Correlations

Denoting the presence of asthma in one twin as A_1 and in the other as A_2, and hay fever correspondingly as H_1 and H_2, six unique correlations for each of the five zygosity groups were calculated: two intraindividual correlations, $r(A_1H_1)$ and $r(A_2H_2)$; two between-twin symptom correlations, $r(A_1A_2)$ and $r(H_1H_2)$; two cross-correlations, $r(A_1H_2)$ and $r(A_2H_1)$ (table 2). The presence of reported asthma and hay fever within an individual was significantly correlated. The correlations of reported asthma and hay fever between each member in a twin pair were higher in the MZ twins than in the DZ twins (A_1A_2, H_1H_2) and were significantly higher among the comparable male MZ pairs than among the female MZ pairs but lower in DZ men than in DZ women (WLS testing of correlation matrices between sexes within each zygosity type: MZ twin pairs [men versus women], $\chi^2_6 = 14.13$, $p = 0.03$; DZ twin pairs [men versus women], $\chi^2_6 = 22.06$, $p =$

TABLE 2

TETRACHORIC CORRELATIONS BETWEEN SELF-REPORTED HAY FEVER AND ASTHMA*†

		Twin 1		Twin 2		
		Hay fever	Asthma	Hay fever	Asthma	
MZ twins						
Twin 1	Hay fever	—	0.51	0.64	0.38	
	Asthma	0.55	—	0.35	0.76	Men
Twin 2	Hay fever	0.59	0.43	—	0.44	(567 pairs)
	Asthma	0.35	0.59	0.56	—	
		Women (1,232 pairs)				
DZ same-sex pairs						
Twin 1	Hay fever	—	0.56	0.11	0.04	
	Asthma	0.47	—	0.20	0.19	Men
Twin 2	Hay fever	0.31	0.13	—	0.61	(352 pairs)
	Asthma	0.17	0.26	0.45	—	
		Women (751 pairs)				
DZ opposite-sex pairs						
Twin 1	Hay fever	—				
	Asthma	0.51	—			
Twin 2	Hay fever	0.26	0.22	—		
	Asthma	0.04	0.23	0.51	—	
		(906 pairs)				

* Women's results in lower triangle; men's results in upper triangles.

† The asymptotic standard errors for these correlations range from 0.04 to 0.10 for the MZ twins and 0.05 to 0.15 for the DZ twins.

0.001). This suggests that there are different causes of variation in women and in men. There was no evidence for any birth order effects on correlations between twins (WLS testing of correlation matrices with constraints that $r[A_1H_2] = r[A_2H_1]$, $r[A_1H_1] = r[A_2H_2]$, χ^2_2 not significant in any zygosity group).

Although there were no significant age effects on prevalence, different etiologic agents acting in each age cohort could lead to different correlation structures. To examine any such effects, tetrachoric correlation matrices for each age cohort were tested by WLS methods to see if they significantly differed from each other. The results showed no significant differences.

Model for Asthma/Wheezing

Path analytic models composed of a unique environmental component, an additive genetic component, and either a nonadditive genetic component or a shared environmental component were fitted to the correlation of asthma between the first and second twins in each of the five zygosity groups (figure 2).

As a further check on the homogeneity of causes of variation over age cohorts, we fitted our gene-environment models separately to each age cohort and then jointly to all 15 groups (five sex/zygosity groups in each of three cohorts). With minor exceptions, the fit of preferred models was homogeneous across cohorts. One advantage of this procedure is that it minimizes any influence of age on estimates of shared environment or nonadditive genetic components. The estimates we obtained of these parameters from the simultaneous fit to all 15 groups were almost identical to those obtained by fitting to only five zygosity groups, combining all ages. Thus, we only present the results from the pooled analysis (table 3).

TABLE 3

RESULTS OF MODEL FITTING FOR REPORTED ASTHMA/WHEEZING

	Amount of Total Variance of Liability Explained				Test of Model Fit		
Model	Additive Genes (%)	Nonadditive Genes (%)	Shared Environment (%)	Unique Environment (%)	χ^2	df	p Value
Women							
1f-Additive and nonadditive genetic influences	45	14	—	41	0.00	0	1.00
2f-Additive genetic influences	59	—	—	41	0.14	1	0.71
3f-Shared environment	—	—	52	49	11.1	1	0.00
Men							
1m-Additive and nonadditive genetic influences	0.01	76	—	24	0.00	0	1.00
2m-Additive genetic influences	74	—	—	26	2.52	1	0.11
3m-Shared environment	—	—	67	32	20.0	1	0.00
Same-sex pairs							
1s-Additive and nonadditive genetic influences	27	40	—	33	6.08	2	0.05
2s-Additive genetic influences	66	—	—	34	7.96	3	0.05
3s-Shared environment	—	—	58	42	37.0	3	0.00
Sex limitation models: all groups							
1x-Additive and nonadditive genes in women	44	16	—	40			
Additive and nonadditive genes in men	18	58	—	24	0.18	1	0.65
2x-Additive genes in women	58	—	—	42			
Additive genes in men	74	—	—	26	4.57	3	0.21
3x-Additive genes in women	59	—	—	41			
Additive and nonadditive genes in men	29	46	—	25	0.61	2	0.74
4x-Additive genes in women	58	—	—	42			
Different additive genes in men*	74	—	—	26	2.66	2	0.27
Hierarchial comparison of models							
Model 2x versus Model 1x					4.39	2	0.13
Model 3x versus Model 1x					0.43	1	0.85
Model 3x versus Model 2x					3.96	1	0.04

* Correlation between genes in women and genes in men = 0.7.

TABLE 4

MODELS FOR COVARIATION OF ASTHMA AND HAY FEVER FITTED TO ALL FIVE TWIN GROUPS ALLOWING DIFFERENT INFLUENCES IN MEN AND WOMEN

Model		Additive Genes	Nonadditive Genes	Unique Environment	Genetic Correlation	Environmental Correlation	χ^2	df	p Value
1. Full model	F	Yes*	Yes	Yes	Yes	Yes			
	M	Yes	Yes	Yes	Yes	Yes	11.8	17	0.81
2. No environmental correlation	F	Yes	Yes	Yes	Yes	No			
between diseases	M	Yes	Yes	Yes	Yes	No	28.4	21	0.08
3. No environmental components	F	Yes	Yes	No	Yes	Yes			
unique to a disease	M	Yes	Yes	No	Yes	Yes	41.0	19	0.00
4. No genetic correlation between	F	Yes	Yes	Yes	No	Yes			
diseases	M	Yes	Yes	Yes	No	Yes	220	21	0.00
5. No nonadditive genetic	F	Yes	No	Yes	Yes	Yes			
component to diseases	M	Yes	No	Yes	Yes	Yes	23.0	23	0.46
6. Nonadditive genetic component	F	Yes	No	Yes	Yes	No			
to diseases in men only	M	Yes	Yes	Yes	Yes	No	13.6	20	0.85
Hierarchical Comparison of Models									
Model 2 versus Model 1							12.1	4	0.02
Model 3 versus Model 1							29.2	2	0.00
Model 4 versus Model 1							208	4	0.00
Model 5 versus Model 1							11.2	6	0.08
Model 6 versus Model 1							1.8	3	0.62
Model 5 versus Model 6							9.4	3	0.02

Definition of abbreviation: df = degrees of freedom.
* Included in model to be tested.

asthma and hay fever, it was necessary to extend our model to the bivariate case. As we were only analyzing two variables in this case, the proportion of variability due to genetic components specific to any one disease cannot be separated out, but the genetic correlation between the two can be estimated. The full bivariate model initially tested consisted of additive and nonadditive genetic components common to asthma and hay fever (genetic atopy), additive and nonadditive genetic components unique to asthma or hay fever, an environmental component shared by asthma and hay fever, and a unique asthma or hay fever environmental component (figure 3). Each model was fitted to all five zygosity groups, permitting the sexes to load differently on each component as had been shown necessary in the univariate analysis of asthma (table 4, Model 1). An initial step of setting the environmental covariation between asthma and hay fever to zero had the effect of causing a significant deterioration in fit of the model (Model 2). When the unique environmental component is removed for asthma or hay fever, this too leads to a poor fit (Model 3). More importantly, the model assuming no common genetic component to both diseases (Model 4) also leads to a significant deterioration of fit. Attempting to fit a model without any nonadditive genetic component (Model 5) did not prove successful, but a nonadditive genetic component for women can be dispensed (Model 6).

Therefore, different parsimonious models for men and women were ultimately selected: for men, the full model; for women, a common additive genetic component and an additive genetic component specific for asthma and/or hay fever. This model fit the data as well as the full model for both sexes [$\chi^2_3 = 13.58 - 11.80 = 1.78$ (not significant, 3 df)]. It led to an estimate of the genetic correlation between the diseases of 0.65 for women and 0.52 for men, and an environmental correlation of 0.33 for women and 0.53 for men. Further removal of parameters led to equally well-fitting, but not significantly better, models—these different alternatives could not be further discriminated.

Discussion

The Questionnaire Items

The design of reliable and valid questionnaires for the diagnosis of asthma has been handicapped by the difficulty of exactly defining the disease in terms of symptoms, and various studies have reached conflicting conclusions about the most appropriate questions to ask (24, 25). In a study of the genetics of asthma, the items used needed to detect those individuals only partially affected by any such trait. The definition we have used is therefore broader than "physician diagnosed asthma." By contrast, the item covering hay fever, by not including an operational definition, would probably have led to an overestimation of the prevalence of this symptom, attributed to confusion with vasomotor rhinitis, especially among women. The high consistency of self-report found for the items in the present study agrees with those reported in the literature (2, 26).

Prevalences

The cumulative prevalences for self-reported asthma or wheezing seen in this study are similar to those seen in other population-based studies in Australia. A survey of adults in rural Western Australia found a point prevalence of asthma of 5.9% and a cumulative prevalence of 9% (5). As much as 28% of these subjects stated they had wheezed at some time in their lives. Salome and colleagues (3) reported a cumulative prevalence of wheezing of 24% in a group of 2,363 Australian schoolchildren and 12% of diagnosed asthma. Because these results are from questionnaires specifically aimed at asthma, recall of nonasthmatic wheezing would be higher in these studies than in the current one, where the items are two among many. The cumulative prevalence of hay fever is in keeping with those reported in Australia (4), though higher than North American (27) or Swedish (12) populations. The excess of women reporting hay fever has also been previously reported and is thought to rep-

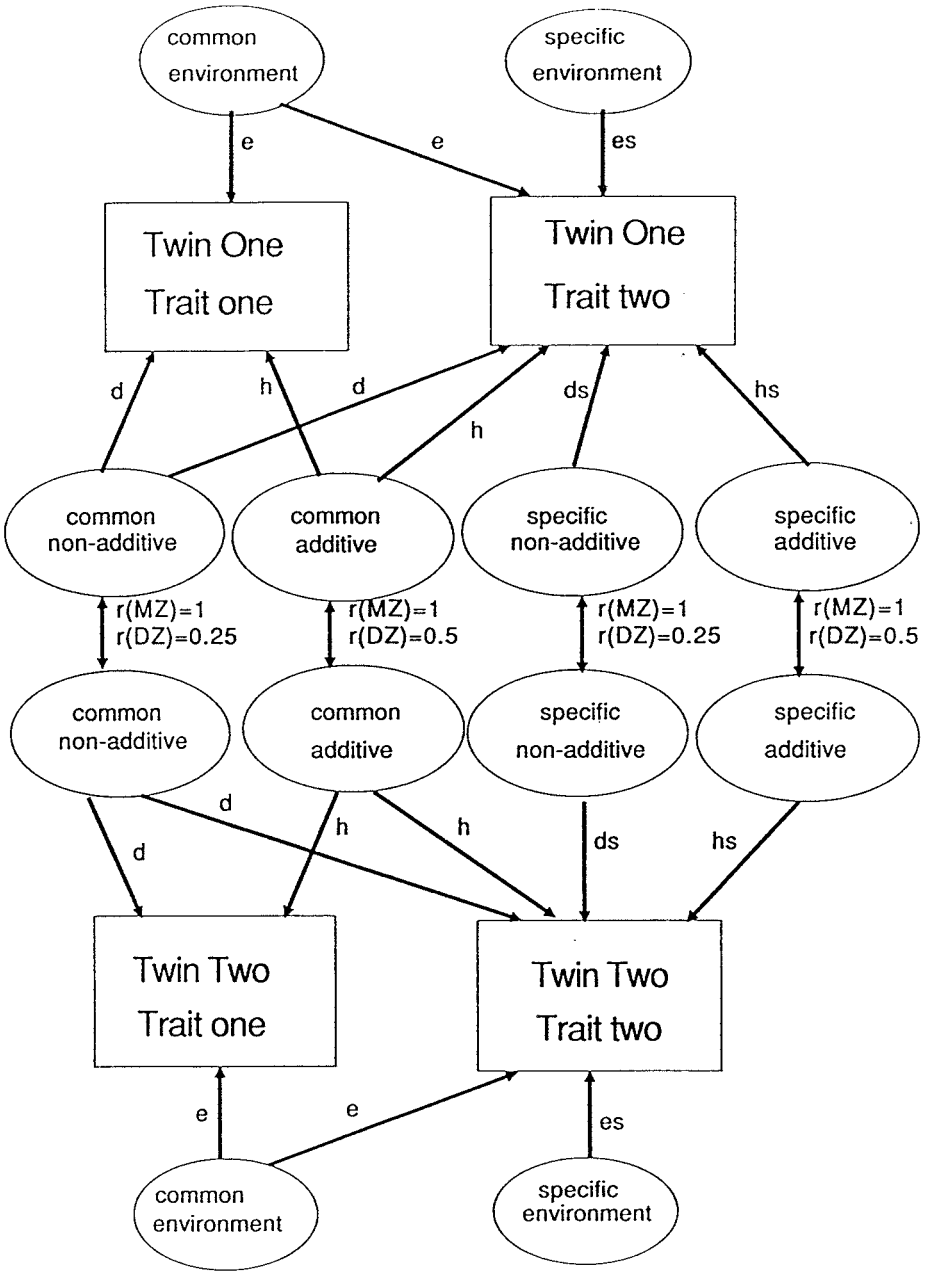

Fig. 3. Path diagram for model combining asthma and hay fever. In the bivariate case, because components unique to one particular disease cannot be identified, only common and specific components of variation can be examined: h = common additive genetic path coefficient; hs = trait-specific, additive genetic path coefficient; d = common nonadditive genetic path coefficient; ds = trait-specific, nonadditive path coefficient; e = common individual-specific, environment path coefficient; es = trait-specific, environment path coefficient.

Initially we fitted the alternative full models to each sex, then to the same-sex pairs, and finally to all five zygosity groups.

Turning first to the female twins, when we examined model 3f, in which all resemblance between twins is due to shared environment, this predicted phenotypic correlations significantly different from the observed correlations on χ^2 testing. Therefore, we rejected this hypothesis. Model 2f, where similarities are due solely to additive genetic effects, led to a fit that was not significantly worse than the full model.

We noted that in men, the nonadditive genetic component made a large contribution to the variance (Model 1m) and that the purely additive model (Model 2m) was almost rejected. The nongenetic model (Model 3m) was definitely rejected.

On extending the analysis to four groups—MZ men, MZ women, DZ men, and DZ women—we had four correlations used to estimate two parameters (h and d) for the full model. This gave a χ^2_2 of 6.1 ($p = 0.047$), which implied that using a model in which the contributions of genetic components were constrained to be the same in each sex led to a poor fit to the observed correlations. Therefore, the next step was to examine sex limitation models, where genetic and environmental influences are allowed to be of different sizes in each sex.

The full sex limitation model, estimating h_f and h_m, d_f and d_m, gave a good fit (Model 1x). When the nonadditive parameter was removed for the women (Model 3x), this led to only a small drop in goodness of fit [χ^2 (df = 2 − 1) = 0.61 − 0.18 = 0.43, not significant]. Removal of the nonadditive genetic component for men, however (Model 2x), led to a significant deterioration in fit. An alternative model (Model 4x) that supposes different genes acting in each sex also gave a good fit but is biologically less explicit than Model 2x. Genetic models, including cigarette intake as an additional cause of asthma, correlated among twins reached an identical conclusion (analysis not shown).

Summarizing the above, the most parsimonious model (Model 2x) seemed to suggest different patterns of inheritance in men and women, men showing evidence of a nonadditive genetic component in comparison with women where only an additive genetic component is evident. Shared environment alone was unable to explain the observed correlations and had to be small compared with nonadditive genetic effects. This led to estimates of heritability for asthma or wheezing of approximately 60% in women and 75% in men.

Model for Hay Fever

Similar models of inheritance were fitted to the five correlations for hay fever. There was no evidence of significant age confounding. Although the pattern of parameter estimates in each sex group was similar to that seen for asthma/wheezing (data not shown), homogeneity χ^2 testing provided no statistically significant evidence of differing effects of genes in men or in women. The preferred model for hay fever, therefore, is composed of additive genetic and unique environmental components acting similarly in both sexes. This gives an estimate of heritability for hay fever of approximately 60%.

Bivariate Model for Asthma/Wheezing and Hay Fever

To examine the relationship between

resent a bias in perception rather than a biologic difference in susceptibility (6, 28). The lack of a significant, positive correlation with age in reported cumulative prevalence may be due to the fact that most individuals develop asthma and hay fever before 20 yr of age or to secular increases of incidence with time or to increased forgetting or denial of disease with age (29).

Birth order might have been expected to demonstrate an effect on the prevalence of asthma due to an association of meconium aspiration or twin-twin transfusion with later respiratory disease (28, 30), more likely to affect the aftercoming twin. The fact that it was not seen in the MZ twins, where genetic factors are held constant, suggests that such perinatal effects are relatively small.

Correlations

The largest twin study previously undertaken to study asthma and allergic disease (12) reported twin case concordance rates equivalent to tetrachoric correlations for self-reported (ever) asthma of approximately 0.65 among MZ twins and 0.25 among DZ twins (7,000 pairs; correlations calculated from the original data). These correlations agree well with the results of the current study (combining the sexes, $r_{MZ} = 0.65$, $r_{DZ} = 0.24$, SE for both = 0.05), even though the prevalence of asthma in the Scandinavian study was only 3.8%. It must be noted that this prevalence is for asthma, whereas the entity measured in our study is asthma or wheezing. The correlations between hay fever in twins observed in the Swedish study were also similar: for MZ twins, it was approximately 0.45, and 0.25 for the DZ twins, whereas for our group it was 0.61 for MZ twins and 0.25 for DZ twins. The correlation within individuals of self-reported asthma and hay fever seen in the present study is consistent with that seen in Australian adults ($r = 0.55$, $n = 8{,}611$; C.A. Mitchell, unpublished data). The similarity of correlations between the current study and the Swedish study is interesting given the large differences in reported cumulative prevalence. One interpretation would be that the intercountry differences in prevalence are due entirely to the shift in the diagnostic threshold from asthma to asthma or wheezing, although the underlying liability distributions are identical. A final point is that the small size of the association between cigarette smoking and asthma and wheeze found in this study is similar to those reported in other studies (27, 29).

Path Models

Although the χ^2 results for the various models should be regarded as guides rather than as exact statements of likelihood, a number of conclusions about the genetics of asthma and hay fever may be made: (*1*) Both diseases have a common genetic component. This acts more nonadditively in men. This finding is interesting because although asthma and hay fever are usually more prevalent in male children, the prevalence among the sexes are equal by adulthood. These sex differences had been thought to be probably genetic in origin (32). We note the sex difference in age of onset and the higher heritability we derive for men compared with women reporting these conditions, but a test of any actual causal association would require more information.

(*2*) There is evidence of covariation of environmental influences on asthma and hay fever, which is consistent with our biologic knowledge of the importance of aeroallergens in each disease. (*3*) Our study was not able to detect a role for an effect of shared environment in explaining the correlations between disease in each member of a twin pair. That is, the resemblances appeared to be mainly due to genetic similarities as opposed to simultaneous exposure to the same household allergens, infective agents, or cigarette smoke, though any small effect of shared environment will appear as additive genetic effects in the analysis.

(*4*) There appear to be environmental influences that affect asthma or hay fever separately. This may represent, for example, a role of respiratory tract infection in the etiology of asthma (33, 34). (*5*) The genetic correlation between both diseases was less than unity, implying that there are additional genetic influences unique to at least one and probably both diseases.

Cookson and colleagues (28, 35) reported evidence of a single dominantly inherited gene located on chromosome 11q12-13 controlling IgE hyperresponsiveness. Within the kindreds they studied, 85% of those diagnosed as carrying this gene suffered some form of allergic disease such as hay fever and 20% were asthmatics. This suggests that 80 to 90% of the variability seen in the expression of asthma in these individuals is controlled by environmental effects and/or by effects of genes at other loci. The findings from the current study provide additional evidence of the view that there are other genes specific to asthma, an interpretation reached in other family studies (8-11, 36).

Limitations

A number of caveats need to be borne in mind when examining the conclusions of our study. (*1*) The definition of asthma used in this research, as in all questionnaire-based studies, may not fully represent the clinical entity of asthma and other wheezy illnesses. Similarly, the already noted bias in the diagnosis of hay fever in women might tend to mask any evidence of nonadditive genetic influences on this disease. (*2*) Although we were unable to demonstrate any significant effect of age on a subject's asthma, there is other evidence that suggests there may have been a secular increase in disease incidence in the last thirty years (37). Because there were small differences in the age distributions in the different zygosity groups (DZ men especially tending to be slightly younger than the other groups) and because not all subjects had passed through the age of risk, there may exist a small degree of age confounding.

(*3*) The classic twin study by its nature lacks power in discriminating the effects of genetic nonadditivity from those of shared environment, the latter usually masking the former. Due to the large number of subjects in the present study, this problem has been avoided, and shared environment should explain no more than $\frac{1}{2}d^2$, but a more precise estimate is unobtainable. All these problems can be minimized by the addition of half-sibling and parental information, and the use of bronchial provocation testing to give objective diagnosis of bronchial hyperresponsiveness (9).

Conclusion

In conclusion, the findings of the present study are consistent with a common genetic influence on asthma and hay fever, supplemented by other genes controlling asthma or hay fever alone. Approximately 40% of the variation in liability to these diseases in this population seemed to be environmental in nature. It is likely that more genes and ultimately gene products will be found to be involved in the etiology of these common diseases.

Acknowledgment

The writers thank Dr. C. A. Mitchell and two anonymous reviewers for useful suggestions made during the writing of the manuscript.

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